REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Examiner Interview Summary

The undersigned would like to thank Examiners Venci and Ceperley for the courtesy extended to herself and Mr. Gerald Swiss (Reg. No. 30,113) during a telephone interview on Thursday, March 1, 2007. During the interview, Applicants reviewed the prosecution history and suggested claim amendments that will further distinguish over the cited art to further the prosecution of the instant application. Specifically, Applicants suggested amending the claims to recite that up to 8 derivatives samples can be produced by the methods of the invention. Further, Applicants suggested introducing the limitations of claims 15 and 16 into the independent claims. These amendments are more thoroughly discussed below.

Claim Amendments

Claims 15 and 16 are canceled.

Claims 4, 6, 8-10, 12-14, 17-18, 21, 28, 32-36 are currently being amended.

Claims 4, 6, 8-10, 12-14, 17, 21, 28, 32-36 are being amended to recite that up to 8 samples can be derivatized.

Claim 17 has been amended to correct the dependency from claim 15, which is now canceled to claims 32 or 33.

Claim 18 is being amended to add the word "molecules" which was inadvertently not included before.

Claim 28, 32-34 and 36 are being amended to limit the differential isotope labeled reagents to contain an aldehyde, selected from formaldehyde and acetaldehyde and a reducing agent. Support for this amendment may be found in original claims 15 and 16.

Claims 28, 32-34 and 36 are also being amended to recite that there are up to 8 combinations of isotopically labeled reagents. Support for this amendment may be found, for example, in the specification, on page 19, paragraph [0097]. Specifically, the specification teaches 8 combinations of isotopically labeled formaldehyde, an aldehyde, and isotopically labeled sodium borohydride, a reducing agent.

For the Office's assistance, a copy of the conformed claims after entry of the amendment is attached hereto as Appendix A.

Applicants submit that no new matter has been added by this amendment and as such, request its entry.

After amending the claims as set forth above, claims 4-14, 17-23 and 32-36 are now pending in this application.

Information Disclosure Statement

Applicants are resubmitting an Information Disclosure Statement herewith that includes a copy of Jue-Liang Hsu, et al. "Stable-Isotope Dimethyl Labeling for Quantitative Proteomics"; Analytical Chemistry, Vol. 75, No. 24, December 15, 2006, pp. 6643-6652.

Applicants request that the Examiner consider this reference.

Claim Rejections under 35 U.S.C. §112 – second paragraph

Claims 4-23 and 32-36 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Specifically, the Office stated that "[t]hroughout the claims, the phrase 'differential isotope labeled reagents' is indefinite. The number of chemically distinct reagents is not clear. The number of isotopically distinct reagents is not clear."

Applicants submit that the phrase 'differential isotope labeled reagents' refers to reagents wherein one of the atoms of the reagent contains an isotope. For example, the reagent could contain an isotope of hydrogen, carbon, oxygen, etc. Applicants have amended the claims to clarify that there may be up to 8 combinations of these reagents. Further, Applicants have amended the claims to clarify that each of the up to 8 combinations of differential isotope labeled reagents contain *two* reagents, an aldehyde selected from formaldehyde and a reducing agent. An example of the "up to 8 combinations" may be found, in the specification, for example, on page 19, paragraph [0097].

The amendments submitted herewith obviate the rejection and as such, Applicants request its withdrawal.

Claim Rejections under 35 U.S.C. §102

Claims 4-15, 17-23 and 32-36 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Aebersold et al. (U.S. Patent 6,670,194).

The Action states that "Aebersold et al. teach a method for the simultaneous quantitative analysis of at least three samples as substantially described. . . Aebersold et al. do not teach a method wherein formaldehyde and acetaldehyde are used." *See*, the Office Action at page 5.

Aebersold et al. refer to the use of "aldehyde and/or ketone reactive groups," however, as correctly pointed out in the Action, there is no specific teaching of formaldehyde nor acetaldehyde. *See,* Aebersold et al., col. 10, lines 37-43. Applicants have amended their claims to recite that one of two the reagents used to label the molecules ***must be*** an aldehyde selected from formaldehyde or acetaldehyde.

As such, Aebersold et al. does not anticipate the claimed invention. Applicants respectfully request withdrawal of this rejection.

Claim Rejections under 35 U.S.C. §103

Claim 16 stands rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Aebersold et al. (U.S. Patent 6,670,194) in view of Vandekerckhove & Gevaert (U.S. Publication 2004/0005633).

The Action states that:

> Aebersold et al. teach a method for the simultaneous quantitative analysis of at least three samples as substantially described. . . Aebersold et al. do not teach a method wherein formaldehyde and acetaldehyde are used. . . However, Vandekerckhove & Gevaert teach the use of deuterated formaldehyde and acetaldehyde. . . in order to induce a mass distinguishable mass shift in peptide analysis. . . It would have obvious for a person of ordinary skill in the art to modify the method of Aebersold et al. with the use of formaldehyde and acetaldehyde because Vandekerckhove & Gevaert teach that such reactions are 'known to proceed in mild conditions' and 'may lead to the incorporation of a predictable number of deuterium atoms.'

Applicants disagree that it would been obvious to modify the method Aebersold et al. with the use of formaldehyde and aldehyde because the formaldehyde and the acetaldehyde do not provide the requisite functionality to arrive at the affinity-labeled protein reactive reagents of Aebersold et al.

Specifically, Aebersold et al. teach affinity-labeled protein reactive reagents that have three portions, namely A-L-PRG, wherein A is an affinity label, L is a linker group and PRG is a protein reactive group. Simply put, acetaldehyde (CH_3-C(=O)-H) and formaldehyde (H-C(=O)-H) do not contain enough atoms or functionality to fall under the A-L-PRG reagents taught by Aebersold et al. It may be that formaldehyde and acetaldehyde might be able to serve as the PRG or perhaps even the L-PRG of Aebersold et al. but there is no possibility of acetaldehyde and formaldehyde serving as the A-L-PRG of Aebersold et al.. In light of this, it

would not have been obvious to modify the teachings of Aebersold et al. (i.e., reagents containing A-L-PRG) in light of the teachings of Vandekerckhove & Gevaert (i.e., using deuterated formaldehyde and acetaldehyde).

Applicants invention as currently claimed employs combinations of isotopically labeled formaldehyde/acetaldehyde and reducing agents. As explained above, the teachings of Aebesold, et al., either alone or in combination with the teachings of Vandekerckhove & Gevaert cannot be modified to arrive at the currently claimed invention.

As such, Applicants invention of only using isotopically labeled formaldehyde and acetaldehyde is not rendered obvious in light of the teaching of these two references.

In the light of the amendments and arguments presented above, Applicant respectfully request withdrawal of this rejection.

Conclusion

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. In the event that this amendment and reply does not place this application in condition for allowance, Applicants would greatly appreciate if the Examiner would contact the undersigned by telephone at 650-251-1104.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37

C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date March 9, 2007 By _____

FOLEY & LARDNER LLP
Customer Number: 38706
Telephone: (650) 251-1104
Facsimile: (650) 856-3710

Lorna L. Tanner
Attorney for Applicants
Registration No. 50,782

APPENDIX A

CONFORMED CLAIMS

Claims 1-3 (canceled)

4. The method as in claims 32 or 33 comprising an additional step of cleaving the up to 8 samples of differential isotope labeled derivatives of molecules into fragments, prior to the step of examining the up to 8 samples of differential isotope labeled derivatives of molecules by mass spectrometry.

5. The method as in claims 32 or 33 comprising an additional step of denaturing the molecules prior to step (ii).

6. The method as in claims 32 or 33 wherein the step of examining the up to 8 samples of differential isotope labeled derivatives of molecules by mass spectrometry comprises introducing the up to 8 samples of differential isotope labeled derivatives of molecules to a mass spectrometer using electrospray ionization.

7. The method of claim 6 wherein the electrospray ionization method is selected from the group consisting of nanospray, pneumatically assisted electrospray, ionspray and turboionspray.

8. The method as in claims 32 or 33 comprising an additional step of separating the up to 8 samples of differential isotope labeled derivatives of molecules into sub-fractions before the step of examining the up to 8 samples of differential isotope labeled derivatives of molecules by mass spectrometry.

9. The method of claim 8 wherein the step of separating the up to 8 samples of differential isotope labeled derivatives of molecules uses a separator selected from the group consisting of 1-D gel electrophoresis, SDS-PAGE, isoelectric focusing, 2-D gel electrophoresis, zone electrophoresis, isotachophoresis, ion exchange chromatography, normal phase chromatography, reverse phase chromatography, hydrophobic interaction chromatography, size exclusion chromatography and any combination of these separators.

10. The method of claim 4 comprising an additional step of separating the fragments after the step of cleaving the up to 8 samples of differential isotope labeled derivatives of molecules and before the step of examining the up to 8 samples of differential isotope labeled derivatives of molecules.

11. The method of claim 10 wherein the step of separating the fragments uses a separator selected from the group consisting of liquid chromatography, high performance liquid chromatography and capillary electrophoresis.

12. The method as in claims 32 or 33 comprising an additional step of analyzing the up to 8 samples of differential isotope labeled derivatives of molecules after the step of examining the up to 8 samples of differential isotope labeled derivatives of molecules by mass spectrometry.

13. The method of claim 12 wherein the derivatives are peptides and the step of analyzing the up to 8 samples of differential isotope labeled derivatives of molecules is selected from the group consisting of collision-induced dissociation in a mass spectrometer operating in MS/MS mode, peptide mass fingerprinting, peptide mapping, Edman sequencing and sequencing by sequential amino acid cleavage.

14. The method of claim 13, comprising an additional step of sequencing the molecules, after the step of analyzing the up to 8 samples of differential isotope labeled derivatives of molecules.

15. (canceled)

16. (canceled)

17. The method as in claims 32 or 33 wherein the reducing agent is selected from the group consisting of a sodium cyanoborohydride, sodium borohydride, dialkyl borane complexes and pyridine borane complexes.

18. The method as in claims 32 or 33 wherein the molecules are selected from the group consisting of cells, cellular extracts, sub-cellular extracts, cellular lysates, peptides, proteins, drugs, toxins, antibodies and pollutants.

19. The method of claim 18 wherein the sample comprises a protein having an amine and the protein is extracted from a cell.

20. The method of claim 19 wherein the amine of the protein is selected from the group consisting of a lysine residue, ornithine residue and a residue at the N- terminal amino group of the protein.

21. The method as in claims 32 or 33 wherein the step of examining the up to 8 samples of differential isotope labeled derivatives of molecules by mass spectrometry utilizes a mass spectrometer selected from the group consisting of:

(i) Fourier transform – Ion cyclotron resonance mass spectrometers (FT-ICR-MS);

(ii) Time of Flight mass spectrometers (TOF-MS, TOF-TOF-MS);

(iii) Ion trap mass spectrometers (IT);

(iv) Quadrupole mass spectrometers (Q-MS and QqQ-MS);

(v) Ion mobility mass spectrometers (IM-MS);

(vi) Quadrupole (or hexapole, octapole)-Time of Flight mass spectrometers (Q-TOF, and Qq-TOF); and

(vii) Ion trap – Time of flight mass spectrometers (IT-TOF).

22. The method of claim 21 comprising an additional step of combining the mass spectrometer with an ionization source.

23 The method of claim 22 wherein the ionization source is selected from the group consisting of electrospray ionization, matrix-assisted laser desorption and ionization (MALDI), field desorption, thermal desorption and laser desorption.

Claims 24-27 (canceled)

28. (withdrawn) A kit comprising (i) up to 8 combinations of differential isotope labeled reagents, wherein each combination contain an aldehyde selected from formaldehyde and acetaldehyde and a reducing agent and each of the up to 8 combinations of differential isotope labeled reagents is isotopically distinct and (ii) instructions to follow the methods of quantitative analysis of any of claims 32 or 33.

Claims 29-31 (canceled)

32. A method for the simultaneous quantitative analysis of up to 8 samples comprising molecules, the method comprising:

(i) providing up to 8 combinations of differential isotope labeled reagents, wherein each combination contains an aldehyde selected from formaldehyde and acetaldehyde and a reducing agent, and each of the up to 8 combinations of differential isotope labeled reagents is isotopically distinct;

(ii) reacting each of the up to 8 samples comprising molecules with one of the up to 8 combinations of differential isotope labeled reagents to produce up to 8 samples of differential isotope labeled derivatives of molecules;

(iii) combining the up to 8 samples of differential isotope labeled derivatives of molecules for examination by mass spectrometry; and

(iv) examining the up to 8 samples of differential isotope labeled derivatives of molecules by mass spectrometry.

33. A method for the simultaneous quantitative analysis of up to 8 samples comprising molecules, wherein each of the molecules has an amine bearing an active hydrogen, the method comprising:

(i) providing up to 8 combinations of differential isotope labeled reagents, wherein each combination contains an aldehyde selected from formaldehyde and acetaldehyde and a reducing agent, and each of the up to 8 combinations of differential isotope reagents is isotopically distinct;

(ii) reacting each of the samples comprising molecules with one of the up to 8 combinations of reagents, wherein the reacting results in a reductive alkylation of the amine of the molecules to alkylamine derivatives of the molecules, to provide up to 8 samples of differential isotope labeled derivatives of molecules that are differentially isotope labeled at an alkylamine;

(iii) combining the up to 8 samples of differential isotope labeled derivatives of the molecules for examination by mass spectrometry; and

(iv) examining the up to 8 samples of differential isotope labeled derivatives of molecules by mass spectrometry

34. A preparation for simultaneous quantitative analysis by mass spectrometry, the preparation comprising up to 8 samples of differential isotope labeled derivatives of molecules, each of the up to 8 samples of differential isotope labeled derivatives of molecules resulting from a reaction of (a) a combination of differential isotope labeled reagents, wherein each combination contains an aldehyde selected from formaldehyde and a reducing agent, and the combination of differential isotope labeled reagents is isotopically distinct with (b) a sample of molecules.

35. The preparation of claim 34 wherein (a) the sample of molecules comprises molecules having an amine bearing an active hydrogen and (b) the up to 8 samples of differential isotope labeled derivatives of molecules comprise derivatives labeled at an alkylamine.

36. A method for the quantitative analysis of up to 8 samples of cellular extracts, each of the up to 8 samples of cellular extracts comprising molecules having an amine bearing an active hydrogen, the method comprising:

(i) providing up to 8 combinations of differential isotope labeled reagents, wherein each combination contains an aldehyde selected from formaldehyde and acetaldehyde and a reducing agent, and each of the up to 8 combinations of differential isotope labeled reagents is isotopically distinct;

(ii) reacting each sample with one of the combinations of differential isotope labeled reagents to produce up to 8 samples of differential isotope labeled derivatives of molecules, wherein the reacting results in a reductive alkylation of the amine of the molecules to alkylamine derivatives of the molecules, such that the up to 8 samples of differential labeled derivatives of molecules are differentially isotope labeled at an alkylamine;

(iii) combining the up to 8 samples of differential labeled derivatives of molecules;

(iii) separating the up to 8 samples of differential labeled derivatives of molecules into fractions;

(iv) enzymatically cleaving the at least three samples of differential labeled derivatives of molecules into fragments;

(v) separating the fragments;

(vi) examining the fragments by mass spectrometry; and

(vii) sequencing the fragments.